REMARKS

After entry of the present Amendment, claims 34-46 and 50-52 are pending in the Application. Claim 34 has been amended to recite that the medium comprises a reproductive cell and that the activated growth factor comprises at least about 75% unbound growth factor. Support for the amendment is found at least at page 3, paragraph 11 and page 7, paragraph 29, accordingly, no new matter is added by way of the amendment.

Applicants have enclosed a Declaration of inventor Kevin Rozeboom, which was originally submitted during prosecution of the parent case, U.S. Application No. 10/081,097, now U.S. Patent No. 6,849,394.

Rejections under 35 U.S.C. § 102(b)

In the Office action, claims 34-40 and 44-46 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 6,150,163 ('163 patent). Claims 34-37 are rejected under 35 U.S.C. 102(b) as anticipated by Naz et al. Claims 34 and 44-46 are rejected under 35 U.S.C. 102(b) as anticipated by Lackey et al. Claims 34-46 and 50-52 are rejected under 35 U.S.C. 102(b) as anticipated Nocera et al.

The rejections are respectfully traversed.

A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully assert that none of the '163 patent, Naz et al., Lackey et al. or Nocera et al. explicitly or impliedly disclose every element of the claimed invention as required by this standard.

The '163 Patent

Independent claim 34 has been amended to recite a composition comprising a reproductive cell and an activated growth factor comprising at least about 75% unbound growth factor. In contrast, the '163 patent discloses "a serum-free, defined cell-culture medium . . . useful in culturing fibroblasts, especially chrondocytes ('163 patent, Abstract). Importantly, no

other cell type, much less a reproductive cell, is described or even mentioned in the reference. Accordingly, the '163 patent does not describe every element of the invention claimed in claim 34 (and, accordingly, claims 35-40 and 44-46 which depend therefrom). In view of the above, withdrawal of the rejection is respectfully requested.

Naz et al.

Claim 34, as amended, recites a composition comprising an activated growth factor comprising at least about 75% unbound growth factor. Naz et al. does not disclose an activated growth factor comprising at least 75% unbound growth factor as claimed. Nevertheless, the Examiner asserts that Naz et al. discloses a "medium supplemented with growth factor [which] is found to be biologically functional as related to reproductive or sperm cells. Thus the growth factor is reasonably expected to be in unbound form or in fully activated form within the meaning of the claims." (Office action, page 3, lines 17-19). The Examiner thus assumes that because a medium is "biologically" functioning, this necessarily means that it inherently comprises at least 75% unbound growth factor.

The Examiner is reminded that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). The Examiner has not met this burden. Indeed, contrary to the Examiner's unsupported assertion that the "biologically" functioning medium of Naz et al. means that the growth factor was in unbound activated form, the teachings of Naz et al. rather suggest that the TGF factors were not activated. Naz et al. analyzed the effects of compositions comprising interferon-α , interferon-γ, TGF-β_1 and TGF-α on sperm motility. (Naz et al., Abstract). Naz et al. note that while TGF- β_1 was related to enhanced synthesis of a 50 KDa protein related to 2-5(A)synthetase "this increase does not affect sperm function." (Page 161, col. 1, lines 11-13). Naz et al. also disclose that "TGF- α neither affected sperm motility nor enhanced the synthetase activity in sperm cells." (Page 161, col. 2, lines 39-40). Naz et al. therefore do not teach an activated growth factor comprising at least 75% unbound growth factor as claimed, either expressly or inherently.

In view of the above, Applicants respectfully assert that claim 34 is allowable. Claims 35-40 and 44-46 each depend from allowable claim 34 and are therefore also allowable. Withdrawal of the rejection is respectfully requested.

Lackey et al.

Claim 34, as amended, requires a composition comprising an activated growth factor comprising at least about 75% unbound growth factor. Lackey et al. does not teach an activated growth factor comprising at least 75% unbound growth factor within the meaning of the present claims. Indeed, Lackey does not even mention an activated growth factor comprising at least 75% unbound growth factor, or that any particular proportion of IGF is in activated form. Nevertheless, the Examiner asserts that Lackey et al. disclose a "medium supplemented with growth factor [which] is found to be biologically functional as related to reproductive or sperm cells. Thus, the growth factor is reasonably expected to be in unbound form or in fully activated form within the meaning of the claims" (Office action, page 4, lines 9-12). The Examiner thus assumes that that because a medium is "biologically" functioning, this necessarily means that it inherently comprises at least 75% unbound growth factor.

As noted above, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). However, not only has the Examiner failed to provide any support for the assertion that the factors used in Lackey would inherently comprise at least 75% unbound growth factor, this is clearly not the case. Lackey et al. disclose the effects of insulin-like growth factors on bovine sperm motility. (Abstract). The effects are based on an efficacy of 100 ng/mL and 250 ng/mL factors over a 6 hour period (page 117, lines 7-8 and page 119, Table 2). In contrast, as is evident from Examples 1-4 of Applicants' specification, Applicants used growth factors at a concentrations several orders of magnitude lower than those used by Lackey et al., and noted improvements in viability over a period of days, rather than hours. Therefore, Lackey et al. do not teach an activated growth factor comprising at least 75% unbound growth factor as claimed, either expressly or inherently.

Accordingly, Lackey et al. does not teach each element of claim 34, and claim 34 is allowable. Claims 44-46 each depend from allowable claim 34 and are therefore also allowable.

Nocera et al.

Claim 34 recites a composition comprising a reproductive cell medium comprising an activated growth factor comprising at least about 75% unbound growth factor. Claim 50 recites a sperm cell medium comprising activated TGFβ-1, activated TGFβ-2, and activated IGF-1.

The Examiner asserts that "The acidified seminal plasma [of Nocera et al.] is a medium physiologically suitable for sperm cells" (Office action at page 5, lines 4-5). However, seminal plasma is not a medium within the context of the application. Accordingly, Nocera et al. does not teach a composition comprising a reproductive cell medium as recited by independent claim 34 or a sperm cell medium as recited by independent claim 50. Moreover, Nocera et al. does not teach a medium comprising an activated growth factor comprising at least 75% unbound growth factor within the meaning of claim 34.

It is evident that the Examiner has improperly construed the claim term "medium." Applicants recognize that claims are given the broadest reasonable construction for the purposes of examination. MPEP 2111. However, the broadest reasonable construction must also be consistent with the Applicants' disclosure and the interpretation that those skilled in the art would reach. MPEP 2111, citing *In re Morris*, 127 F.3d 1048 (Fed. Cir. 1997). Applicants respectfully assert that the Examiner's construction of the claims is not reasonable, as it is not consistent with either Applicants' disclosure or the interpretation that would be applied to the claims by those of skill in the art.

Applicants' specification defines "sperm cell medium" as "any medium used for the collection, holding, processing, in vitro fertilization, sexing, culturing, or storing (including long-term cryopreservation) of mammalian, avian, or piscian sperm cells, and includes both solid and liquid compositions, as well as solid compositions that are reconsistituted or mixed with a liquid carrier, such as water, for use." Page 3, paragraph 11. This definition clearly excludes seminal plasma, which would not be appropriate for any of the claimed media functions. Moreover, the

specification clearly distinguishes semen (seminal fluid) from media in several contexts. For example:

> Boar *semen* is generally diluted or extended with a suitable storage *medium*...the culture *medium* serves to increase the total volume of the sample. Page 1, paragraph 4 (emphasis added).

> Many specific *media* formulations are known or are available commercially, including...extenders for preserving *semen.* Page 3, paragraph 12 (emphasis added).

Thus, the context of the application makes clear that storing and maintaining sperm beyond its normal viability for a number of purposes are functions of cell media not served by seminal fluid alone. Moreover, throughout the specification, the terms "semen" and "media" are not used interchangeably, as they would be if they were meant to be mutually inclusive terms.

The definition in the specification is in agreement with the art-accepted usage of "medium." As clearly evidenced by the Declaration of Kevin Rozeboom, submitted in the parent application, and resubmitted herewith, one of skill in the art would not consider seminal plamsa or ejaculate to be a reproductive or sperm "cell medium." The terms are not understood to be synonymous, nor is seminal fluid considered cell media. See Rozeboom Declaration at paragraph 6.

Applicants respectfully assert that, when "reproductive cell medium" and "sperm cell medium" are properly construed, it is clear that the rejection of independent claims 34 and 50 as anticipated by Nocera et al. is improper, as not all elements of the rejected claims are taught.

Moreover, the rejection of claim 50 is improper because Nocera et al. does not teach activated IGF-1. The Examiner asserts that the seminal fluid of Nocera et al. would inherently comprise activated IGF-1, because Lackey et al. discloses that "seminal plasma also contains IGF-1." Office action, page 5, line 1. Again, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). However, neither

Lackey et al. nor Nocera et al. teaches, or even mentions, activated IGF-1. The Examiner has provided no basis in fact for the assumption that the acidified seminal fluid of Nocera et al. would necessarily contain activated IGF-1. The rejection of claim 50 is therefore improper, as not every element of the claim is taught.

Accordingly, claims 34 and 50 are allowable. Claims 35-46 and each depend from allowable claim 34, and claims 51-52 each depend from allowable claim 50 and are therefore also allowable.

Rejection under 35 U.S.C. § 103(a)

In the Office action, claims 34-46 and 50-52 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,150,163. Claims 34-46 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naz et al. and Lackey et al. taken with Nocera et al.

A *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143). Applicants respectfully submit that the Office action has failed to set forth a *prima facie* case of obviousness as all the requirements for a *prima facie* case have not been met.

The '163 Patent

Applicants submit that the Office action has failed to set forth a *prima facie* case of obviousness, because the '163 patent, taken alone or in combination with knowledge generally available to one of skill in the art, does not teach or suggest the subject matter of independent claims 34 or 50 (much less dependent claims 35-46 and 51-52).

Independent amended claim 34 requires a reproductive cell and a growth factor selected from the group consisting of activated TGFβ-1, activated TGFβ-2, and activated IGF-1 wherein

the activated growth factor comprises at least about 75% unbound growth factor. All elements of claim 34 are not taught or suggested, or even mentioned by '163 patent. First, the composition of claim 34, as amended, requires a reproductive cell. As discussed above, the '163 patent discloses a serum-free, defined cell-culture medium useful in culturing fibroblasts, especially chrondocytes (see, e.g. Abstract, claim 11) and does not teach or suggest a medium useful for culturing reproductive cells. Secondly, amended claim 34 requires an activated growth factor, and further requires that the activated growth factor comprise at least 75% unbound growth factor. In contrast, the '163 patent does not teach or suggest a composition comprising any activated growth factor, let alone one comprising at least 75% unbound growth factor. Nor has the Examiner indicated where any such teaching may be found either in the '163 reference or in knowledge generally available to one of skill in the art.

The rejection is also improper because one of skill in the art would not be motivated to modify the teachings of the '163 patent to arrive at the claimed invention. The '163 patent provides no motivation to modify its teachings to include in a composition a reproductive cell or an activated growth factor comprising at least 75% unbound growth factor, as recited in claim 34. The '163 patent does not motivate the skilled artisan to include a combination of activated TGFβ-1, activated TGFβ-2, and activated IGF-1 in a sperm cell medium, as recited in claim 50. The citation in the Office action of *In re Pinten, In re Susi* and *In re Crocket* is inappropriate in the present situation. While it is true that it is obvious to combine two or more ingredients, each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for a third purpose, that is not the instant case. The '163 patent does not teach the use of activated growth factors for <u>any</u> purpose. The '163 patent merely discloses that the use of "TGF-β1 <u>or</u> TGF-β2 and IGF-1 satisfy the growth factor requirement for this differentiation process [of human articular chrondocytes that have de-differentiated]" (col. 7. lines 19-25). This disclosure provides no motivation to use both TGF-β1 <u>and</u> TGF- β2 in combination with IGF-1 in a sperm cell medium.

In addition, the Office action does not establish a *prima facie* case of obviousness with respect to claims 34 and 50, because one of skill in the art would not have a reasonable expectation that the media described in the '163 patent, which is taught to be useful for culturing fibroblasts and inducing differentiation of chrondocytes, could be successfully used to culture a

reproductive cell (as recited in claim 34) or a porcine sperm cell (as recited in claim 50). Importantly, chrondocytes and fibroblasts differ in many respects from reproductive cells. Fibroblasts are diploid cells, whereas reproductive cells are haploid. Fibroblasts proliferate, whereas reproductive cells are preprogrammed for cell death. Reproductive cells are notoriously sensitive to media components, whereas fibroblasts are relatively hardy. The compositions and uses of the media of the '163 patent and the instant claims are so disparate that one of skill in the art would have no reasonable expectation of success in the claimed invention based on a media specifically formulated to promote chondrocyte differentiation.

Accordingly, a *prima facie* case of obviousness has not been established with respect to independent claims 34 and 50. Claims 35-46 and 51-52 depend from claims 34 and 50 respectively, and therefore are also not obvious over the '163 patent for at least the reasons cited above. For these reasons, it is respectfully requested that the rejection of the claims as obvious over the '163 patent be withdrawn.

Naz et al. and Lackey et al. taken with Nocera et al.

Applicants submit that the Office action has failed to set forth a *prima facie* case of obviousness of the rejected claims, because Naz et al. and Lackey et al., whether taken together or in combination with Nocera et al., do not teach or suggest the subject matter of independent claims 34 or 50 (much less dependent claims 35-46 and 51-52). Nor would one of skill in the art be motivated to combine the teachings of the cited references, or have a reasonable expectation of success for the claimed combination.

Claim 34 and dependent claims 35-46

A *prima facie* case of obviousness has not been established with respect to independent claim 34 (or claims 35-46 which depend therefrom), because the cited references do not teach or suggest every element of amended claim 34. Claim 34 requires a reproductive cell and a growth factor selected from the group consisting of activated TGFβ-1, activated TGFβ-2, and activated IGF-1 wherein the activated growth factor comprises at least about 75% unbound growth factor. None of the references teach or suggest a composition comprising an activated growth factor comprising at least 75% unbound growth factor as claimed.

Naz et al. does not teach, suggest, or even mention an activated growth factor comprising at least 75% unbound growth factor. Indeed, the TGF-β factors of Naz et al. were found to have no effect on sperm motility and capacitation, suggesting that they were not activated. Naz et al. is silent with respect to any proportion of unbound growth factor present. Lackey et al. also does not teach or suggest a composition comprising a reproductive cell and a medium comprising a growth factor comprising at least 75% unbound growth factor. As discussed above, the concentrations of growth factors used by Lackey et al. are several orders of magnitude higher than those of the present invention, suggesting that the growth factors of Lackey were not activated. As with Naz et al., Lackey et al. is also silent with regard to any proportion of unbound growth factor present.

The secondary reference, Nocera et al., fails to cure the deficiencies of the Naz et al. and Lackey et al. references. Nocera et al. does not teach or suggest a medium comprising an activated growth factor comprising at least 75% unbound growth factor. Although Nocera et al. teaches activated TGF-β_1 in seminal fluid, as discussed above, it does not teach or suggest a composition comprising a medium. Moreover, Nocera et al. contains no teaching or suggestion that any proportion of the TGF-β described therein comprises unbound growth factor, let alone a growth factor comprising at least 75% unbound growth factor. Nocera et al. also does not teach, suggest, or even mention IGF-1. Accordingly, all elements of claim 34 (and dependent claims 35-46) are not taught or suggested by the cited references.

Moreover, the Examiner has not shown that one of skill in the art would be motivated to modify or combine the teachings of the cited references to arrive at the claimed invention. It is well-established that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills,* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Absent any suggestion in the references to make the combination, the Examiner has, in effect, employed impermissible hindsight to reconstruct the claimed methods.

The Examiner asserts that motivation is provided "because the physiologically suitable conditions provided by seminal plasma include growth factors that are presently claimed and because the prior art teaches incorporation of growth factors TGF beta and IGF into artificial cell

culture media intended for sperm cells." Office action, page 7, lines 11-14. However, this statement is conclusory and inaccurate. Other than this conclusion, the Examiner has not indicated where in the prior art suggestion or motivation to combine the reference teachings can be found. Only the "roadmap" provided by the present specification, leads one of skill in the art to the invention recited in claim 34. Therefore, the rejection is improper.

Lackey et al. teaches a composition comprising IGF-1, but does not teach, suggest or even mention TGF-β. In contrast, neither Nocera et al. nor Naz et al. teach anything regarding IGF-1, much less that IGF-1 may be activated, or a mechanism for doing do. Accordingly one of skill in the art would not be motivated to modify or combine the teachings of Lackey et al., Naz et al. and Nocera et al.

Therefore, the cited references provide no motivation to modify or combine their teachings to include a reproductive cell and an activated growth factor comprising at least 75% unbound growth factor in a composition as recited in claim 34.

Even assuming, *arguendo*, that the necessary motivation was taught by the references, none of the references indicate that the skilled artisan would have a reasonable expectation of success with respect to the claimed invention. Nocera et al., far from teaching media compositions suitable for reproductive cells, seeks to elucidate the role of particular components of seminal fluid. Merely teaching that a particular claimed element is a component of human seminal plasma is not sufficient to teach that use of these elements in media would successfully achieve the benefits of the claimed compositions. Furthermore, Naz et al. teach that TGF-β "does not affect sperm motility and capacitation." (Page 162, col. 1, last line to col. 2, lines 1-3). None of the cited references provides one of skill in the art with any reasonable expectation that the reference teachings could be successfully combined to arrive at Applicants' claimed invention.

Accordingly, a *prima facie* case of obviousness has not been established with respect to independent claim 34. Claims 35-46 depend from claim 34, and therefore are also not obvious over the cited references for at least the reasons discussed above. It is respectfully requested, therefore, that the rejection of claims 34 and 35-46 as obvious over Naz et al. and Lackey et al. in view of Nocera et al. be withdrawn.

Claim 50 and dependent claims 51-52

Claims 50 and 51-52 were rejected as being obvious over Naz et al. and Lackey et al. taken with Nocera et al. However, as discussed above for claim 34, one of skill in the art would not have motivation to combine the references. None of the references provide any motivation to combine their teachings to arrive at a sperm cell medium comprising activated TGF-β1, activated TGF-β3 and activated IGF-1 as recited in claim 50. Moreover, as discussed above for claim 34, one of skill in the art would also not have a reasonable expectation of success with respect to the claimed combination.

Even assuming *arguendo* that the references are properly combined and that a reasonable expectation of success exists, the references still do not teach or suggest each of the elements of claims 50 and 51-52. Independent claim 50 recites a sperm cell medium for porcine sperm cells which comprises activated TGFβ-1, activated TGFβ-2, and activated IGF-1. The cited references fail to teach or suggest every element of claim 50. Naz et al. does not teach or suggest incorporating activated TGF-β1 in a sperm cell medium, does not teach or suggest the use of TGF- β2 in a sperm cell medium, and does not mention IGF-1 at all. As discussed above, the TGF growth factors used by Naz et al. were found to either not affect sperm function, or to have no effect on sperm motility, suggesting they were not activated. Page 162, col. 2.

Lackey et al. does not teach, suggest, or even mention TGF-β or activated IGF-1, let alone a sperm cell medium comprising activated TGF-β1 in combination with activated TGFβ-2 and activated IGF-1. As discussed above, the concentrations of growth factors used by Lackey et al. are several orders of magnitude higher than those of the present invention, suggesting that the growth factors of Lackey were <u>not</u> activated.

The secondary reference, Nocera et al., fails to cure the deficiencies of Naz et al. and Lackey et al. because it does not teach, suggest, or even mention IGF-1, let alone that IGF-1 may be activated or a mechanism for doing so. Moreover, as discussed above, the seminal fluid of Nocera et al. is not a "medium" as that term is properly construed. Nocera et al. does not teach or suggest incorporating activated TGF-β in any medium, let alone a composition comprising a sperm cell medium comprising activated TGF-β1 in combination with activated TGFβ-2 <u>and</u> activated IGF-1.

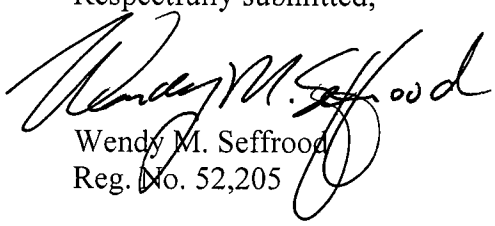
Accordingly, a *prima facie* case of obviousness has not been established with respect to independent claim 50. Claims 51-52 depend from claims 50, and therefore are also not obvious over the cited references for at least the reasons discussed above. Claims 51-52 may be patentable for additional reasons not discussed herein. It is respectfully requested, therefore, that the rejection of claims 50 and 51-52 as obvious over Naz et al. and Lackey et al. in view of Nocera et al. be withdrawn.

This response is accompanied by the fee required under 37 C.F.R. 1.17(a)(1). No other fee is believed due in connection with this submission. In the event that any fee is due, please charge or credit Deposit Account No. 50-0842 for such fee.

CONCLUSION

In view of the foregoing, reconsideration and allowance of claims 34-46 and 50-52 is respectfully requested. The Examiner is encouraged to contact the undersigned by telephone at the Examiner's convenience should any issues remain with respect to the Application.

Respectfully submitted,



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